Hypoglycemia in Type 2 Diabetes: An Underappreciated Management Challenge

- A Practical Case-Based Approach for Overcoming Barriers in the Primary Care Setting -

Canadian Heart Research Centre

Disclosure of Potential Conflict of Interest

Dr. Luciana Parlea

Speaker honoraria - Abbott, Astra Zeneca, BMS, Bayer, Boehringer-Ingelheim, Lilly, Merck, Novo Nordisk, Sanofi-Aventis

Program Development

This program was planned by the Canadian Heart Research Centre, a not-for-profit academic organization to achieve scientific integrity, objectivity, and balance.

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This program was made possible through the financial support of Merck Canada Inc. The opinions expressed herein are those of its authors and do not necessarily reflect the views and opinions of Merck Canada Inc.

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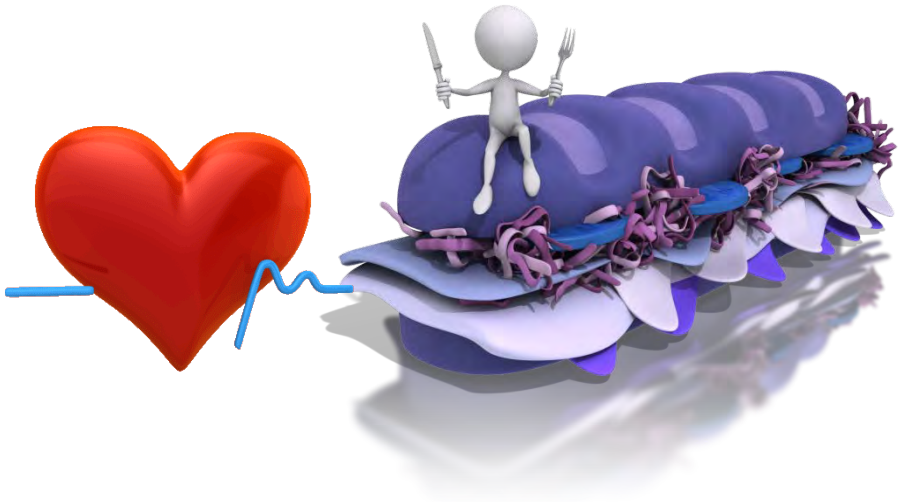
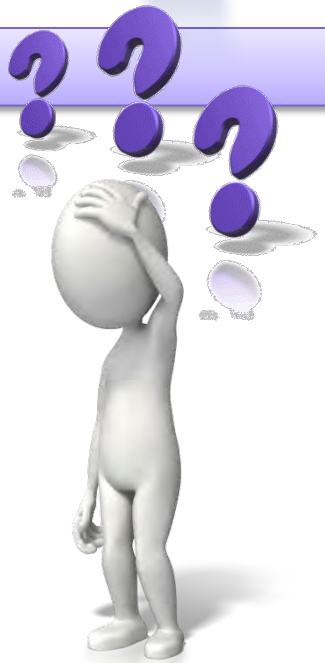
Learning Objectives

- **Upon completion of this program participants will be able to:**
  - ✓ *Recognize hypoglycemia and describe its signs and symptoms*
  - ✓ *Describe the 3 phases of treatment of hypoglycemia*
  - ✓ *Name the causes of hypoglycemia*
  - ✓ *Discuss the impact of hypoglycemia on patients (acute and chronic)*
  - ✓ *Evaluate how the different antihyperglycemic therapies affect glycemic control, risk for hypoglycemia, as well as other risk factors as part of monotherapy and combination therapy*
  - ✓ *Develop practical strategies to reduce hypoglycemia in clinical practice*

I am having hypoglycemia **RIGHT NOW**.
What would I be feeling ?





Definition of Hypoglycemia

1. Development of neurogenic or neuroglycopenic symptoms

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty Concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision Changes
Nausea	Difficulty Speaking
	Dizziness

2. Low blood glucose (<4 mmol/L if on insulin or secretagogue)
3. Response to carbohydrate load

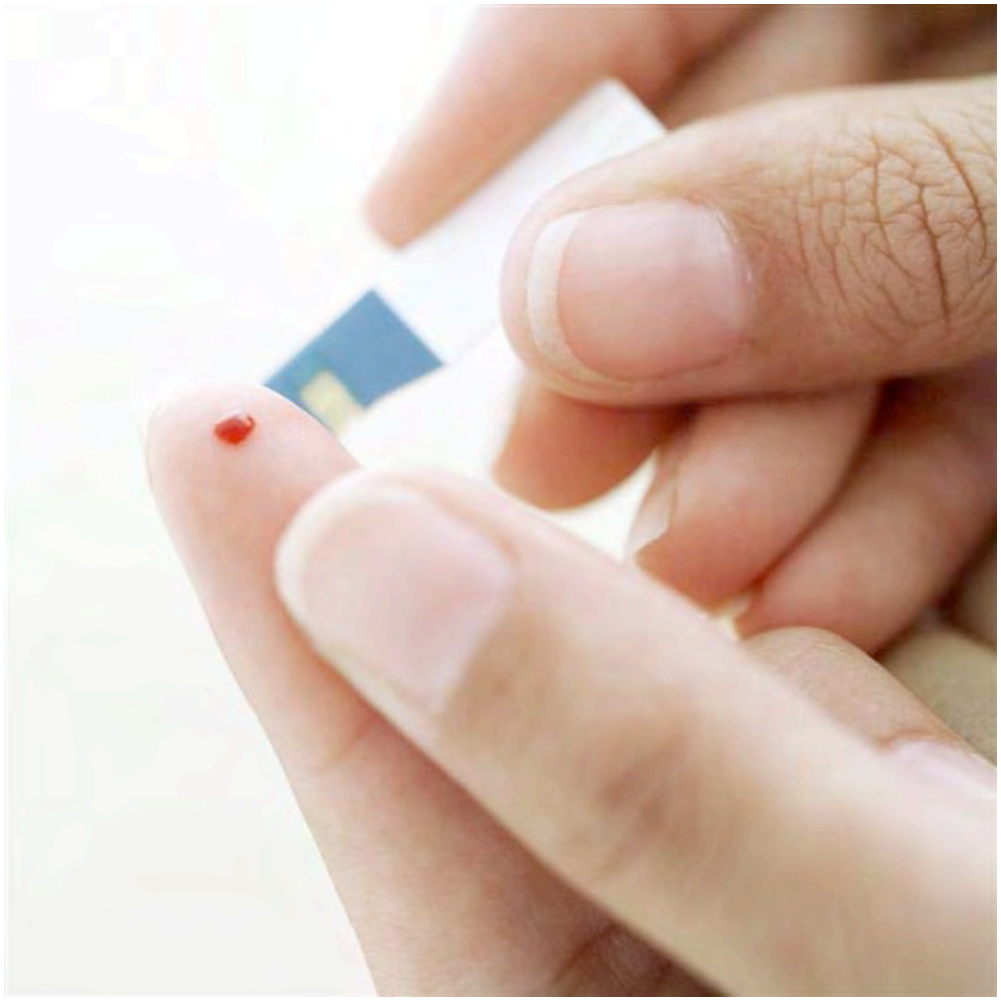
Canadian Diabetes Association Clinical Practice Guidelines. *Can J Diabetes* 2008;32(Suppl 1):S62

Clinical Definition of Hypoglycemia

- **Mild**
  - Autonomic symptoms present
  - Patient able to self-treat
- **Moderate**
  - Autonomic and neuroglycopenic symptoms
  - Patient able to self-treat
- **Severe**
  - Requires the assistance of another person
  - Includes: coma and seizure, episodes treated with IV dextrose or glucagon, or episodes requiring administration of oral carbohydrate by another
- **Hypoglycemia Unawareness**
  - Cognitive symptoms without autonomic symptoms

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes*. 2008

What should be done **RIGHT NOW ?**



I am symptomatic with a capillary glucose of 3.2 mmol/L.

NOW WHAT ??

3 Phases of Hypoglycemia Treatment

1. Acute
2. Intermediate
3. Future

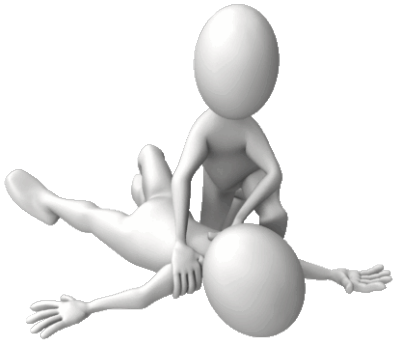
Acute Phase

CONSCIOUS PATIENT

- Oral carbohydrate (glucose or sucrose tablets/solution)
  - 15 g if not severe
  - 20 g if severe (<2.8 mmol/L or needs assistance)
- Retest after 15 minutes
- Repeat 15 g carbohydrate if blood glucose is <4.0 mmol/L

UNCONSCIOUS PATIENT

- Glucagon 1 mg SC or IM



Canadian Diabetes Association Clinical Practice Guidelines. *Can J Diabetes* 2008;32(Suppl 1):S62

Acute = 15g CHO* + 15 minutes recheck

¾ cup OJ

3-4 glucose tablets

3 packs sugar

6 LifeSavers

1 tablespoon of honey

**** CHO – Carbohydrate Food Choices***

Canadian Diabetes Association Clinical Practice Guidelines. *Can J Diabetes* 2008;32(Suppl 1):S62

Intermediate Phase

"To prevent repeated hypoglycemia, once the hypoglycemia has been reversed, the person should have the **usual meal or snack that is due at that time of the day**.
If a meal is >1 hour away, **a snack (including 15 g of carbohydrate and a protein source)** should be consumed"

Canadian Diabetes Association Clinical Practice Guidelines. *Can J Diabetes* 2008;32(Suppl 1):S62

Future

1. Why did it happen?
2. How do I prevent it?

Causes of Hypoglycemia

- Too little food
- Too much activity
- Too much circulating insulin (endogenous or exogenous)

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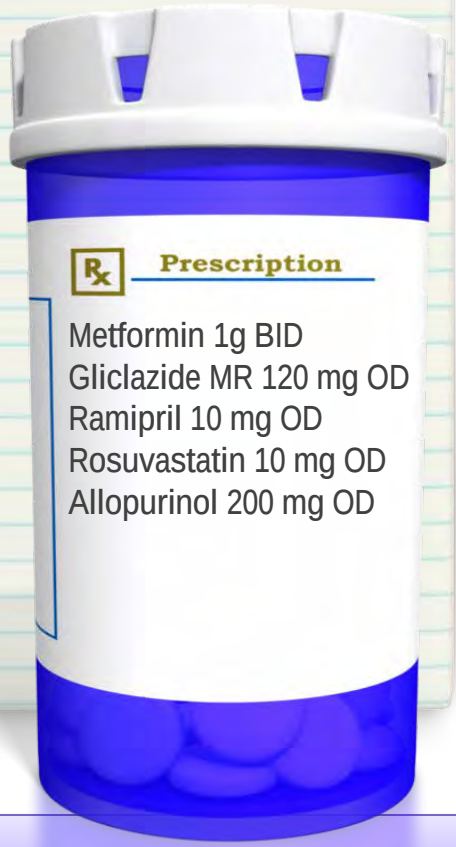
Add an agent best suited to the individual (agents listed in alphabetical order):

Class	Relative A1C lowering	Hypo-glycemia	Weight	Other therapeutic considerations	Cost
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓	Improved postprandial control, GI side effects	$$
Incretin agents:					
DPP-4 Inhibitors	↓↓	Rare	neutral to ↓		$$$
GLP-1 receptor agonists	↓↓ to ↓↓↓	Rare	↓↓	GI side effects	$$$$
Insulin	↓↓↓	Yes	↑↑	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue:					
Meglitinide	↓↓	Yes	↑	Less hypoglycemia in context of missed meals but usually requires TID to QID dosing	$$
Sulfonylurea	↓↓	Yes	↑	Gliclazide and glimepiride associated with less hypoglycemia than glyburide	$
TZD	↓↓	Rare	↑↑	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Weight loss agent (orlistat)	↓	None	↓	GI side effects	$$$

64 year old taxi driver
T2DM x 10 years
No known
cardiovascular disease



Weight: 96 KG
Body Mass Index: 30
Heart Rate: 88 BPM
Blood Pressure: 130 / 80 mmHG
Fundi normal
Abdo benign
Reduced monofilament sensation both feet

A1C 6.1%;
Creatinine 90 umol/L

Questions to Consider

1. Could Robert be having hypoglycemia?
2. What are Robert's risk factors?
3. What would you ask Robert?
4. What will you do about it?
5. Why is hypoglycemia important?

Why is hypoglycemia important ?

Potential Clinical Consequences of Severe Hypoglycemia

- Brain death[1]
- ECG changes that have been associated with[2]
  - Ventricular arrhythmias
  - Sudden death
- Nonfatal cardiac sequelae such as myocardial infarction[3]
- Stroke[3]
- Motor vehicle and other accidents[3]
- Autonomic failure leading to unrecognized hypoglycemia[4]
- Employment limitations[3]

1. Cryer PE. *J Clin Invest*. 2007;117:868–870.
2. Landstedt-Hallin L et al. *J Intern Med*. 1999;246:299–307.
3. Frier BM. *Diabetes Metab Res Rev*. 2008;24:87–92.
4. Cryer PE et al. *J Clin Invest*. 2006;116:1470–1473.

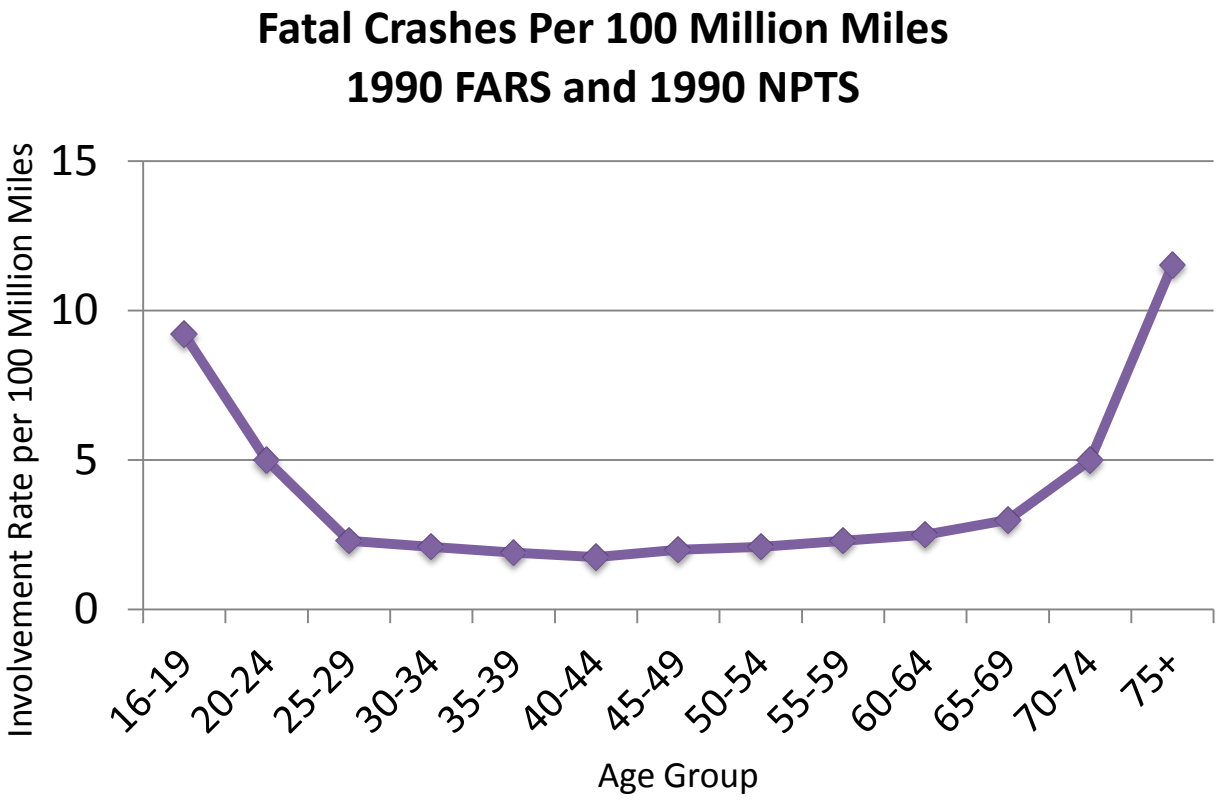
Do people with diabetes have more car accidents ?

Impact of Diabetes on Accident Rates

Reference	Years	N	Type	RR Accident	RR Violation	Comment
Ysander	1952-61	250	1,2	0.65	0.76	per 100 drivers per year: not adjusted for driving exposure;
Ysander	1955-64	219	1,2	0.58	0.97	per 100 drivers per year: not adjusted for driving exposure;
Waller	1960-63	257	1,2	1.78	1.39	per million miles per year
Crancer	1961-67	7676	1,2	1.18	1.07	per 100 drivers per year: not adjusted for driving exposure;
Davis	1970	108	1,2	1.04	1.44	per 100 drivers per year: not adjusted for driving exposure;
De Klerk	1971-79	8623	1,2	1.52	-	Hospital Crash Admissions
Songer	1983-84	127	1	2.00	-	per 100 drivers per year
		121	1	2.66	-	per 100 drivers per million miles
Eadington	1979-87	166	1	0.54	-	per million miles
Stevens	1981-86	354	1,2i	1.01	-	per 1.5 milliom km
Hansotia	1985-88	484	1,2	1.32	-	per 100 drivers per year: not adjusted for driving exposure;
Koepsell	1987-88	234	2	2.47	-	Injury per 100 drivers; matched for miles driven
Gresset	1988-89	121	2	1.01	-	per 100 drivers per year: not adjusted for driving exposure;
		18	1	1.13	-	
Mathiesen	1991-94	7535	1,2	0.13		per 100 drivers per year ; 29% response rate; selection bias

Begg IS, Yale JF, Houlden RL, Rowe RC, McSherry J, Canadian Journal of Diabetes 27(2): 128-140, 2003

Accident Rates in the General Population



The University of Michigan Transportation Research Institute
Ann Arbor, Michigan 48109-2150

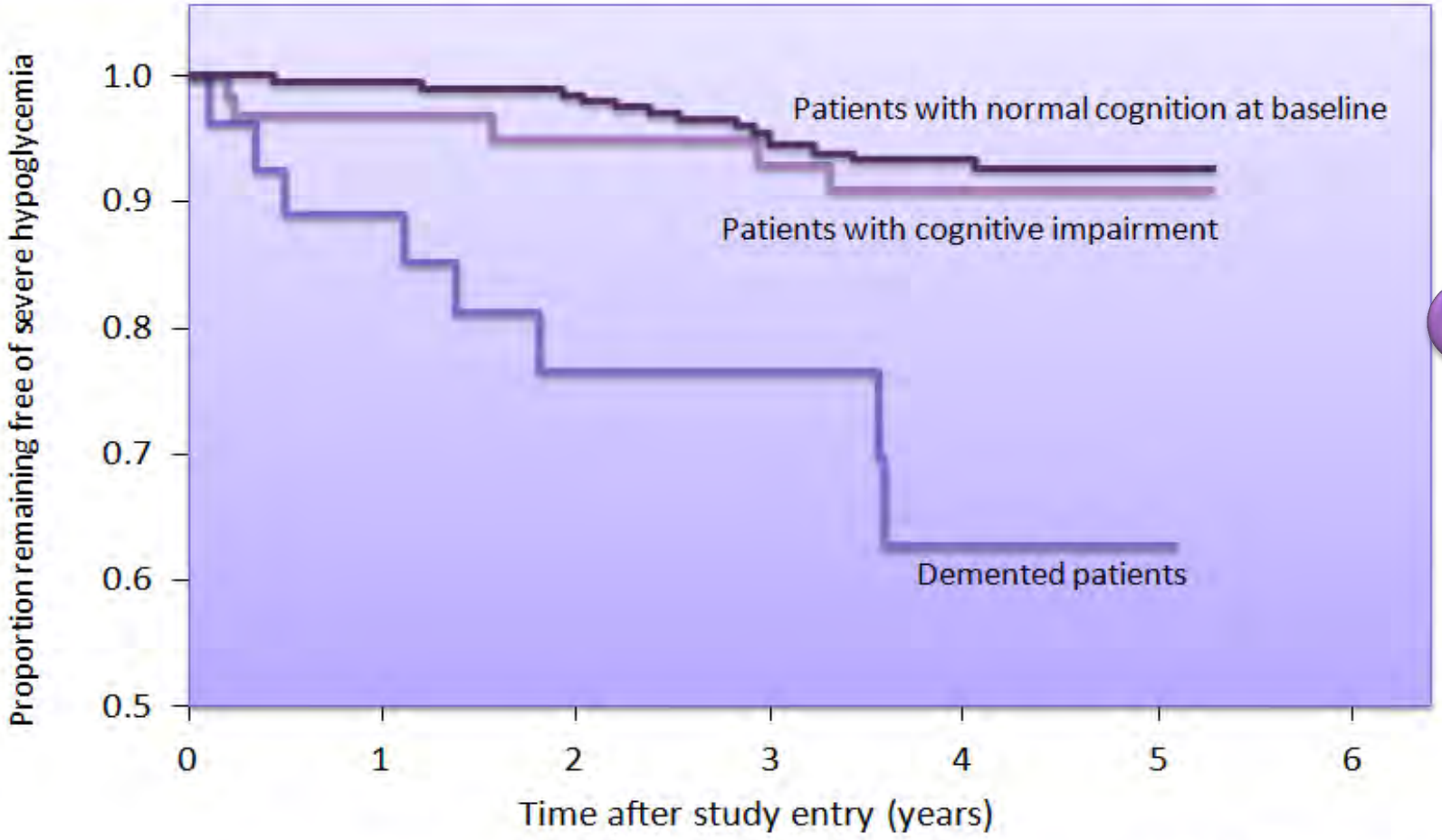
Driving Guidelines

- Requirement for driving license and diabetes vary from province to province
- Requirements for professional versus private are different
- Any driver at risk of hypoglycemia (on secretagogues or insulin) should not drive if less than 5 mmol/L
- Any driver at risk of hypoglycemia should carry blood glucose testing equipment in car and test immediately if hypoglycemia is suspected
- Any driver at risk of hypoglycemia should carry the proper treatment of fast acting carbohydrate easily accessible in the vehicle
- Drivers should wait for 45 minutes before recommencing driving after treatment of a hypoglycemic episode

Iain S. Begg et al . *Canadian Journal of Diabetes*. 2003;27(2):128-140.

Diabetes and Dementia

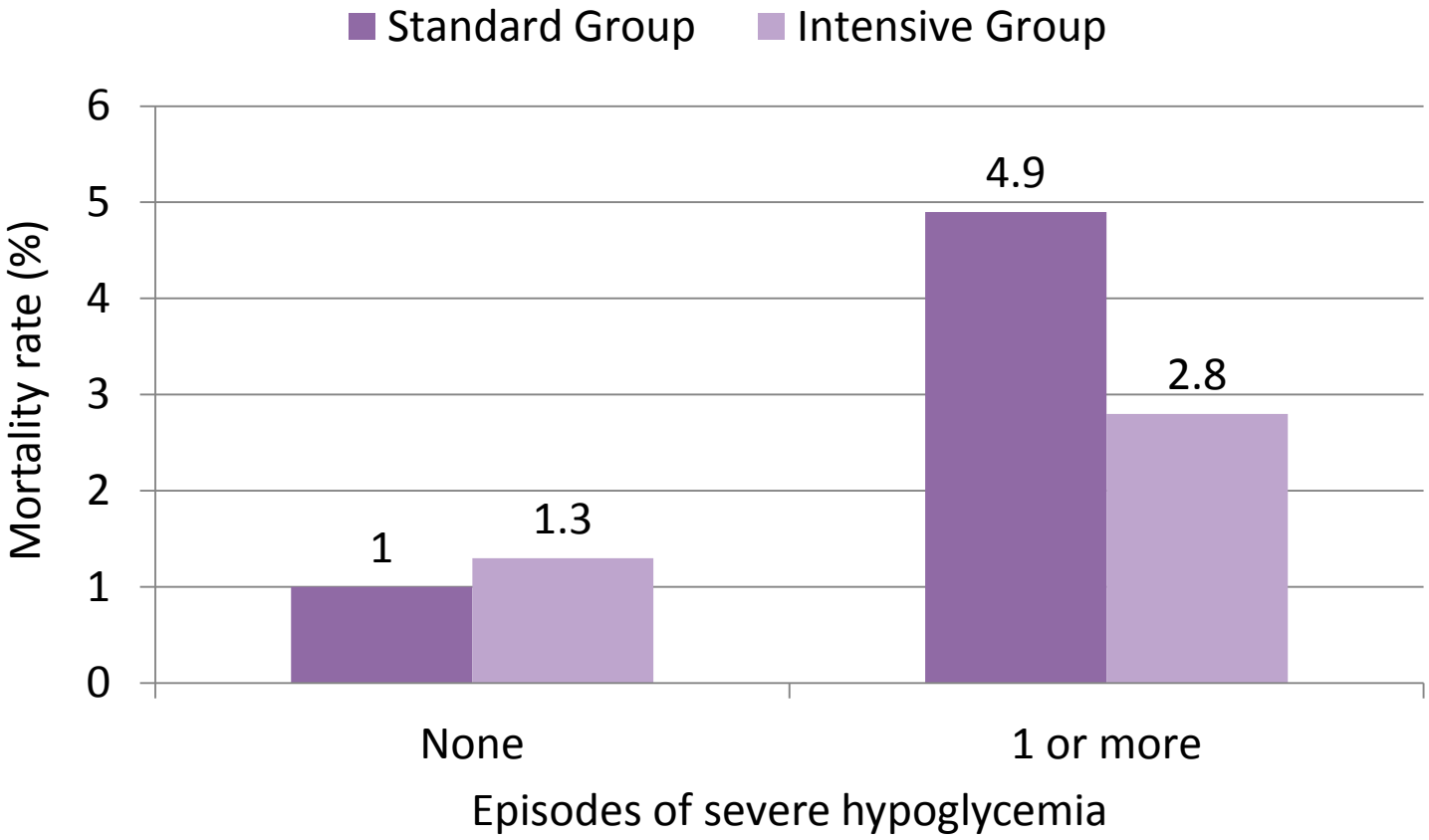
Fremantle Diabetes Study: Dementia Increases Risk of Future SH



Bruce DG et al. *Diabetologia*. 2009;52:1808-15

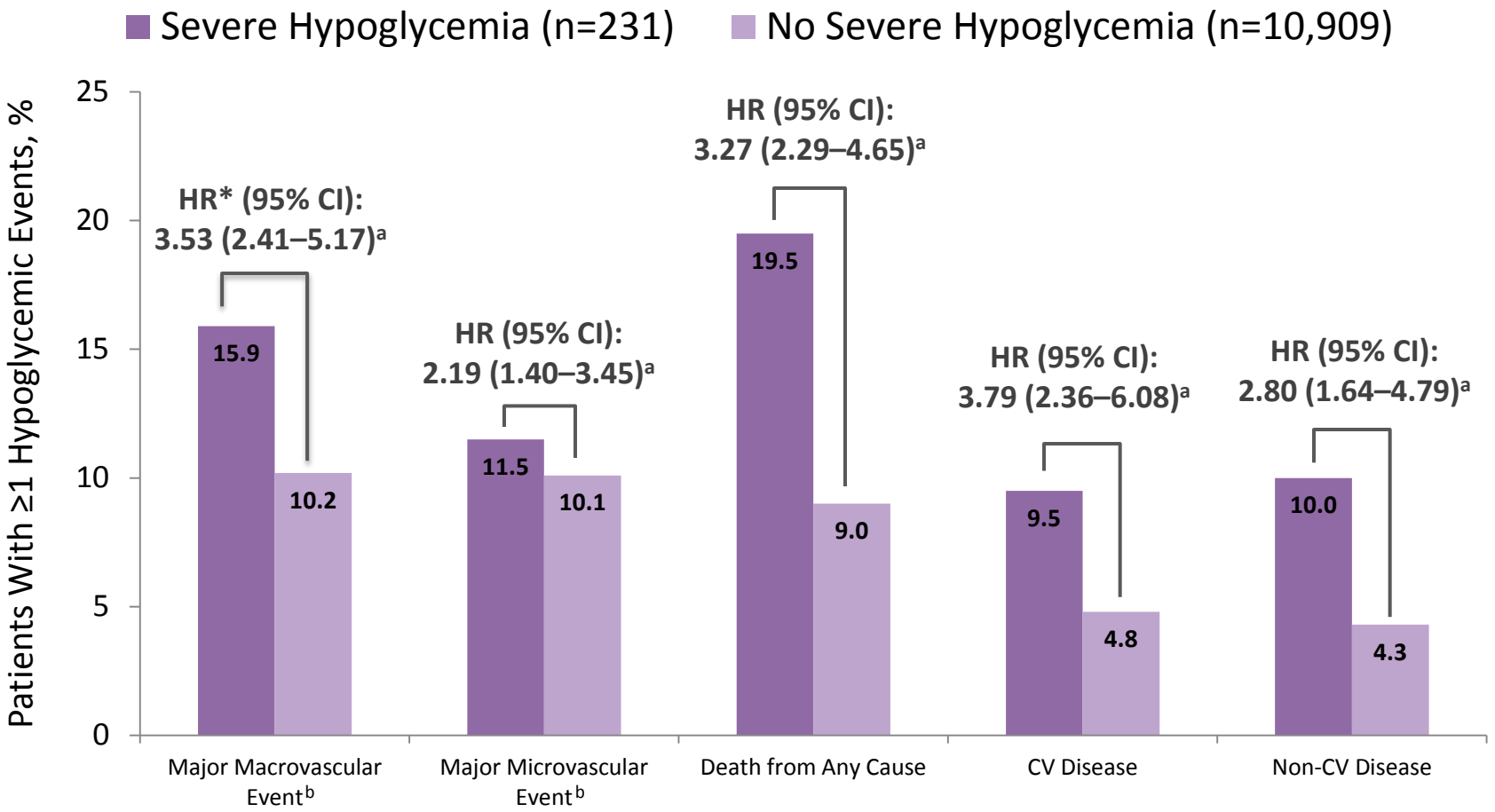
ACCORD: Mortality Rates in Patents with Severe Hypoglycemia Requiring Medical Assistance

Annualized mortality rates (% per year) in patients with ≥ 1 episode of severe hypoglycemia requiring medical assistance and in those with no such episodes in the ACCORD trial



Yakubovich N et al. *Circulation*. 2011;123:342-48

ADVANCE: Severe Hypoglycemia Was Associated With Adverse Clinical End Points and Death[1]



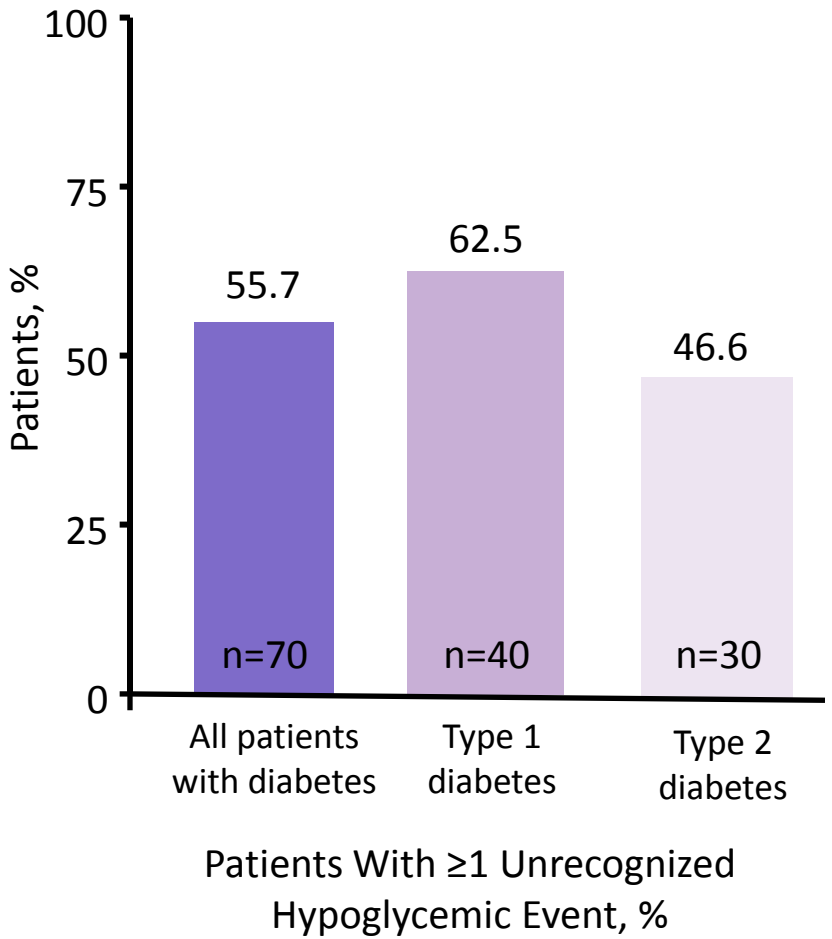
ADVANCE=Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation; CI=confidence interval; CV=cardiovascular; HR=hazard ratio. aAdjusted for multiple baseline covariates. bPrimary end points. Major macrovascular event=CV death, nonfatal myocardial infarction, or nonfatal stroke; major microvascular event=new or worsening nephropathy or retinopathy

* HR: Hazard Ratio

1. Zoungas S et al. N Engl J Med. 2010;363:1410–1418.

Are there other consequences of hypoglycemia?

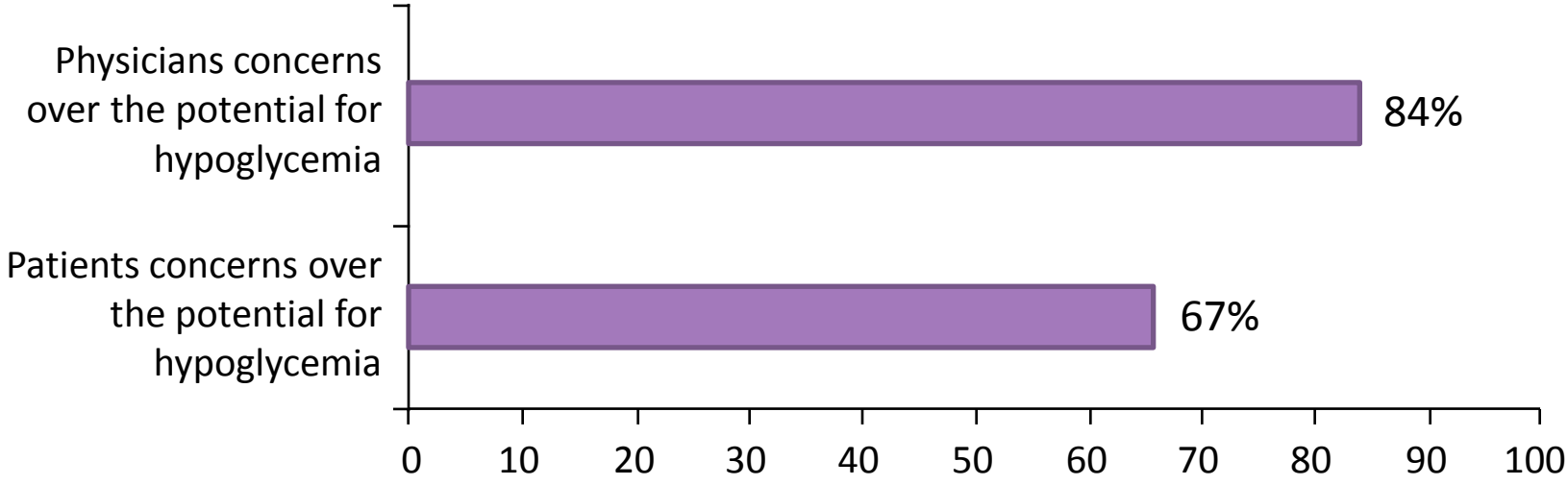
Asymptomatic Episodes of Hypoglycemia May Go Unreported



- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by continuous glucose monitoring[1]
- Other researchers have reported similar findings[2,3]

1. Copyright © 2003 American Diabetes Association. Chico A et al. *Diabetes Care.* 2003;26(4):1153–1157. Reprinted with permission from *The American Diabetes Association.*
2. Weber KK et al. *Exp Clin Endocrinol Diabetes*. 2007;115(8):491–494.
3. Zick R et al. *Diab Technol Ther*. 2007;9(6):483–492.

Hypoglycemia is a Barrier to Effective Management



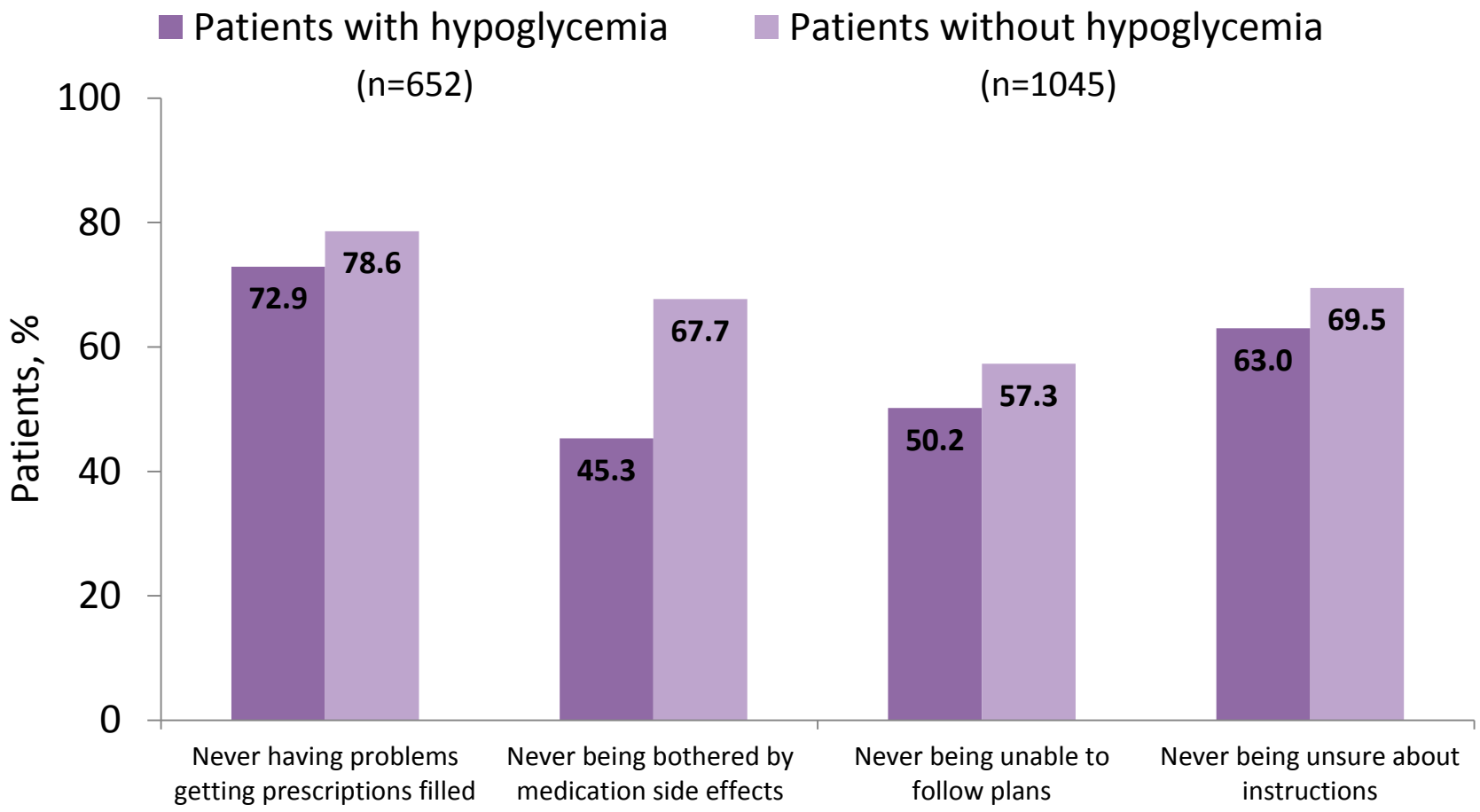
Peyrot et al. GAPP Survey Results. ADA 2011

The Cost and Burden of "Minor" Hypoglycemia

Reduced Well Being	Reduced Productivity	Increased Treatment Cost
▪ Increased anxiety	▪ Average productivity loss is ~$2,300/person/year	▪ Blood glucose testing goes up: 5.6 extra tests within 7 days after hypoglycemia (~$1/strip)
▪ Fear of repeated events compromising glycemic control	▪ Following a nocturnal hypo: 23% arrive late/ miss work, 32% miss a meeting/do not finish a task on time	▪ Risk of suboptimal insulin dose* (25% of patients reduce dose)
▪ Lower quality of life and need for lifestyle changes (e.g., reduced driving)	▪ 15 hours of work is lost	▪ 25% contact a health care professional after an episode

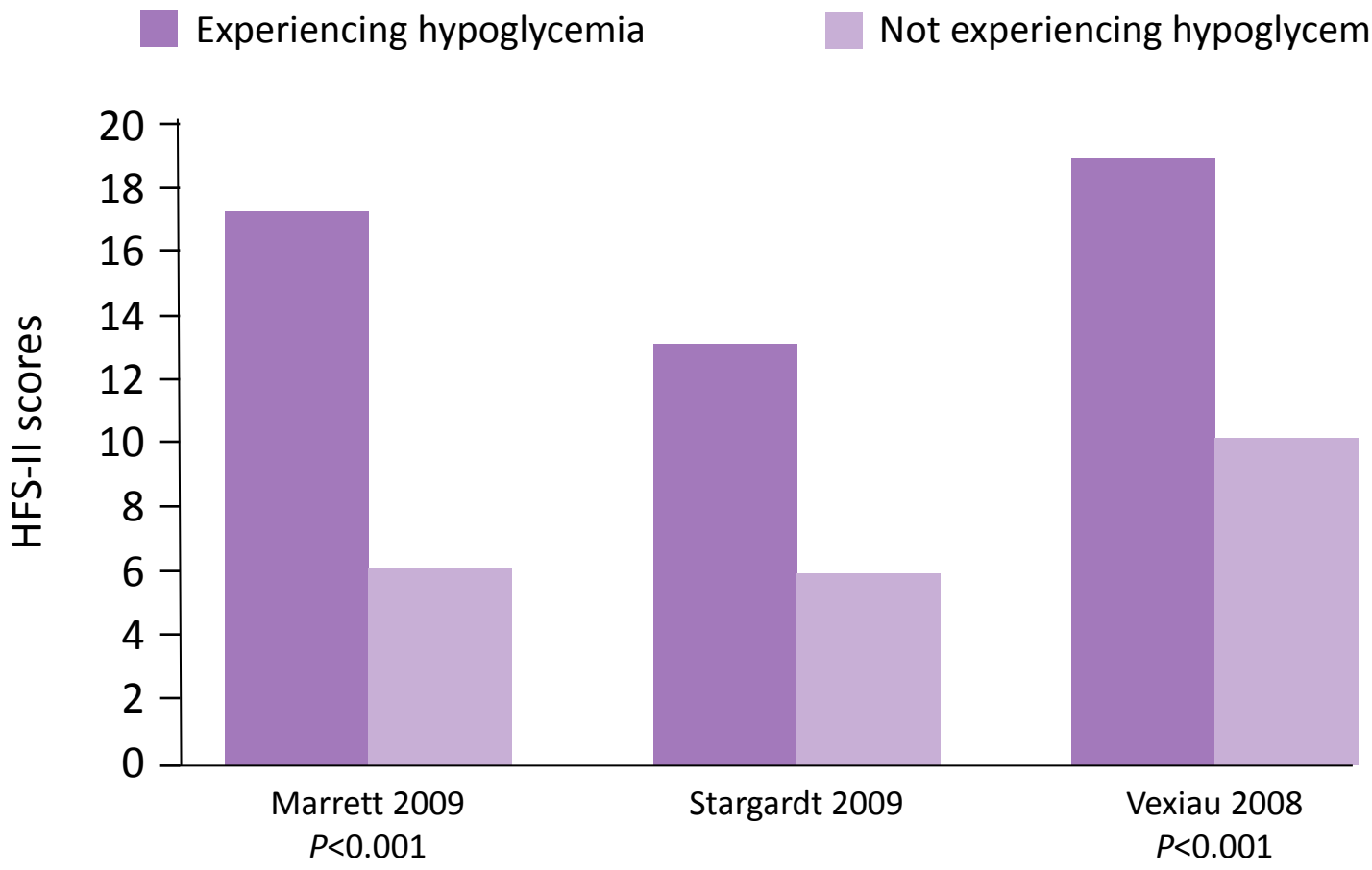
Brod M et al. *Value In Health* 2011; 5:665-71

Decrease in Treatment Adherence Is Associated With the Presence of Hypoglycemic Symptoms



Álvarez Guisasola FA et al. *Diab Obes Metab.* 2008;10 (suppl 1):25–32.

Experience of Hypoglycemia is Associated with Increased Fear of Hypoglycemia



Zhang Y et al. *JCOM* 2010; 17(12):547-57

Hypoglycemia Is Associated With Increased Health Care Costs[1]

- A retrospective cohort study of inpatients with diabetes compared those who developed laboratory evidence of hypoglycemia after 24 hours of hospitalization to those who did not develop hypoglycemia during their entire hospital stay

Base-case analysis (blood glucose <3.9 mmol/L)

Hospital Outcomes, mean	Patients With Hypoglycemia		Patients Without Hypoglycemia		Between-Group Difference or Odds Ratio (unadjusted)[a]	P
	n	Mean Value	n	Mean Value		
Length of hospital stay, d	8234	11.7	95,579	5.1	6.6	<0.001
Hospital mortality, %	7994	4.8	93,012	2.3	2.12[a]	<0.001
Discharged to skilled nursing facility, %[b]	7787	26.5	93,134	14.5	1.83[a]	<0.001
Total hospital charges, 2006 $	6020	85,905	72,681	54,038	59%	<0.001

[a]Difference is shown as the percentage difference for charges, mean difference in days for length of stay, odds ratio for hospital mortality, and odds ratio for discharge to SNF.

[b]Patients who were admitted to the hospital from a SNF were excluded from this analysis.

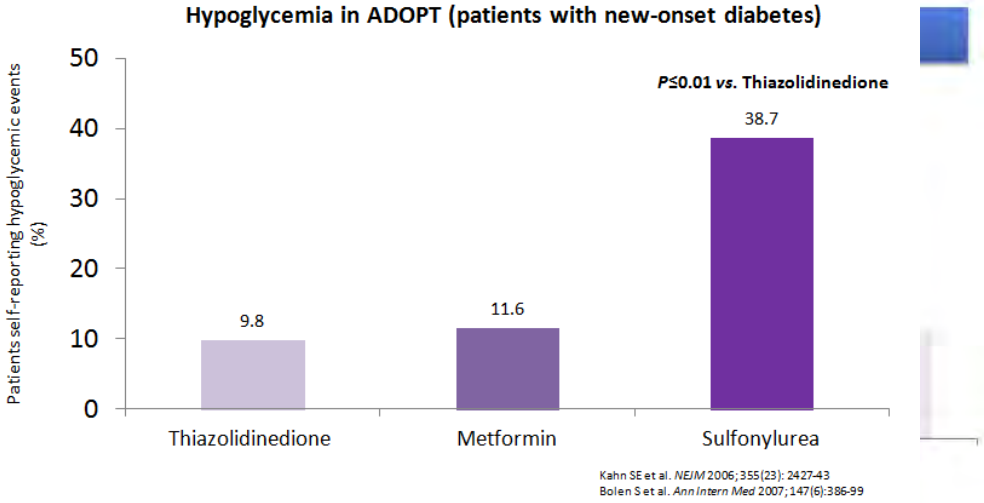
1. Copyright © 2009 AACE. Curkendall SM et al. *Endocr* Pract. 2009;15(4):302–312. Reprinted with permission from the *AACE*.

Prevention of Hypoglycemia

- **If possible, use agents that cause less hypoglycemia**
  - **Incretin agents before secretagogues**
  - **Gliclazide rather than glyburide**
  - **Basal analogue insulin rather than NPH**
- **If elderly, assess cognitive function**
  - If dementia present, simplify therapy
- **Assess renal function**
  - Adjust therapy as needed

Type 2 Diabetes Therapies

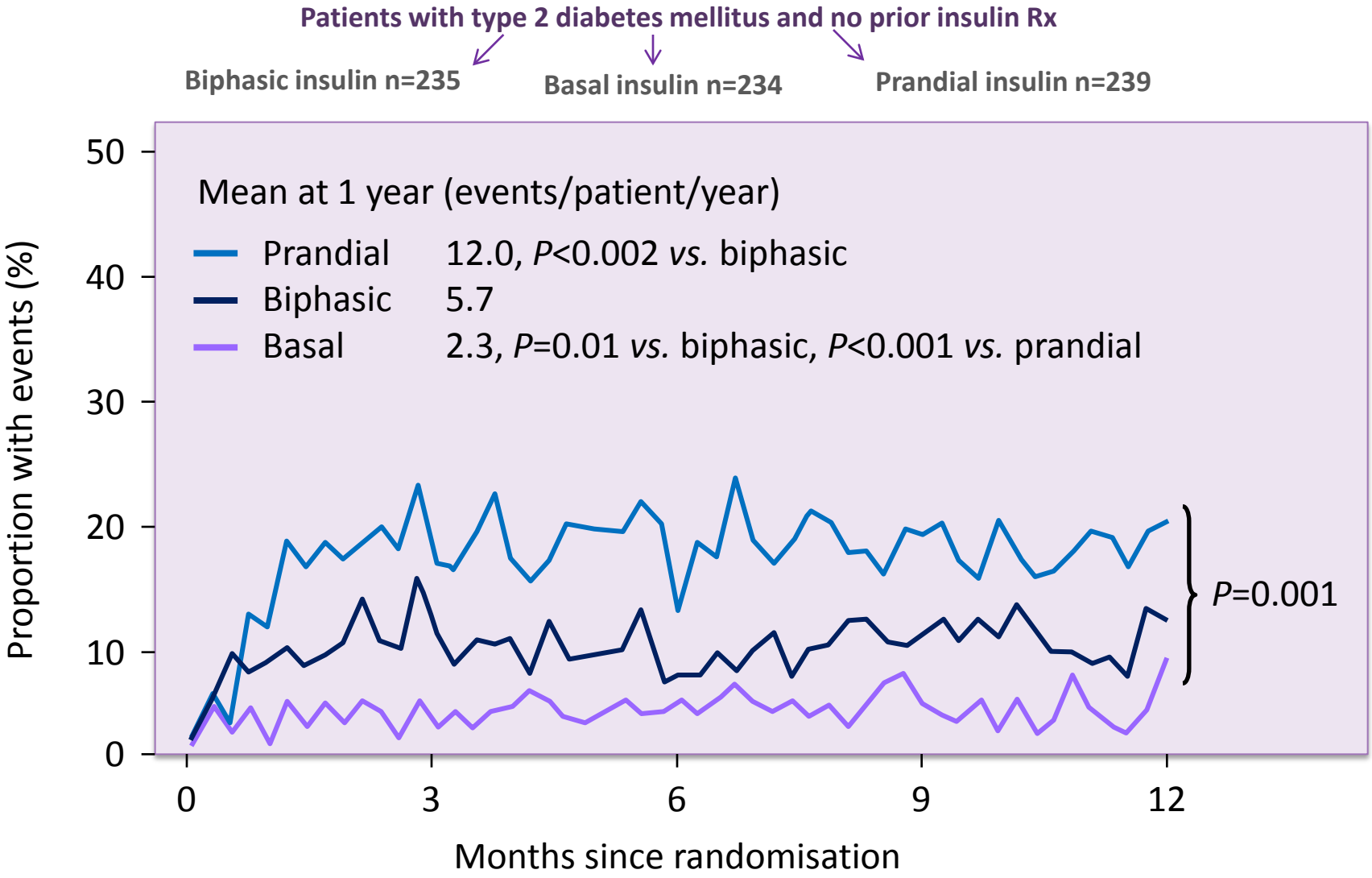
Class	Agent	Hypos
Alpha-glucosidase Inhibitors	Acarbose (GlucoBay)	No
Biguanides	Metformin (Glucophage)	No
DPP-4 Inhibitors	Linagliptin (Trajenta)	No
	Saxagliptin (Onglyza)	No
	Sitagliptin (Januvia)	No
GLP-1R Agonists	Exenatide (Byetta)	No
	Liraglutide (Victoza)	No
Insulins	Analog Insulin	++++
	Human Insulin	+++++
Meglitinides	Nateglinide (Starlix)	++
	Repaglinide (GlucoNorm)	+++
Sulfonylureas	Gliclazide (Diamicron)	++
	Glimepiride (Amaryl)	++
	Glyburide (Diabeta)	+++
Thiazolidinediones	Pioglitazone (Actos)	No
	Rosiglitazone (Avandia)	No



1. Riddle et al. Diabetes Care 2003;26(11):3080-6
2. Philis-Tsimikas et al. Clin Ther 2006;28(10):1569-81

4T Study:

When Initiating Insulin: Less Hypoglycemia with a Basal Regimen



Holman RR et al. *NEJM* 2009; 361:1736-47

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Mini-Cog Instructions

- 3 minute test to screen for cognitive defects in elderly
- 2-3 times faster than MMSE (Mini-Mental State Examination)
- Not affected by language, ethnicity or socioeconomic level

Borson S. The mini-cog: a cognitive "vitals signs" measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry* 2000; 15(11):1021

Mini-Cog Test

1. Remember these 3 words:
   - Blue
   - Apple
   - Train

2. Draw a clock with the arms at 11h10

3. What are the 3 words?

Borson S. The mini-cog: a cognitive "vitals signs" measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry* 2000; 15(11):1021

Mini-Cog Interpretation

- 0 word retained = Cognitive deficit
- 1 or 2 words retained → Examine the clock
  - Abnormal clock = Cognitive defect
  - Normal clock = No cognitive defect
- 3 words retained = No cognitive defect
  - No need to look at the clock

Borson S. The mini-cog: a cognitive "vitals signs" measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry* 2000; 15(11):1021

What To Do in Presence of Cognitive Defect?

- Consultation in geriatrics
- Adherence to medication
  - Pill boxes
  - Simplify therapy, particularly insulin therapy
  - Get the family involved
- Nutrition support

Consider A1C 7.1-8.5% if …

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- Limited life expectancy
- High level of functional dependency
- Extensive coronary artery disease at high risk of ischemic events
- Multiple co-morbidities
- History of recurrent severe hypoglycemia
- Hypoglycemia unawareness

- Longstanding diabetes for whom is it difficult to achieve an A1C ≤ 7%, despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy

Prevention of Hypoglycemia

- **If possible, use agents that cause less hypoglycemia**
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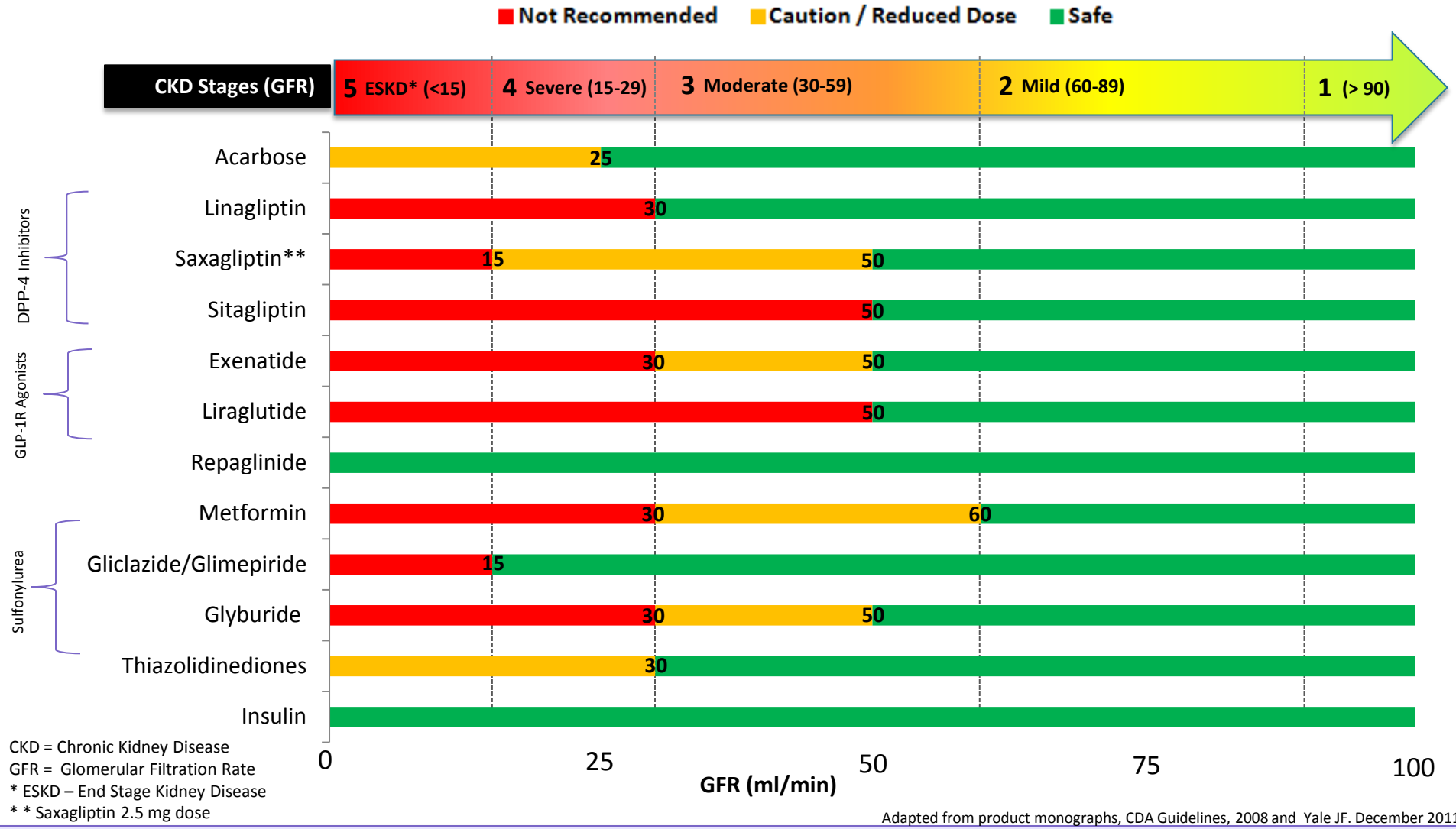
Antihyperglycemic Agents in Kidney Disease



CKD = Chronic Kidney Disease
GFR = Glomerular Filtration Rate
* ESKD – End Stage Kidney Disease
* * Saxagliptin 2.5 mg dose

Adapted from product monographs, CDA Guidelines, 2008 and Yale JF. December 2011

Based on Canadian product monographs as of Nov 13, 2011

People in whom Hypoglycemia should be Particularly Avoided

- **Employment**
  - Truck driver, taxi driver, bus driver, pilot, train engineer, heavy machinery

- **Isolation**
  - People living alone, particularly if eldery

- **Elderly** with cardiovascular disease

Risk Factors of Hypoglycemia

- Insulin secretagogues and insulin
- Elderly
- Dementia
- Long duration of diabetes
- Prior episode of severe hypoglycemia
- Hypoglycemia unawareness
- Renal failure
- Delayed or skipped meal
- Alcohol intake
- Physical activity

1. CDA. Can J Diabetes 2008; 32:S29–S31.
2. Workgroup on Hypoglycemia, American Diabetes Association. Diabetes Care. 2005;28(5):1245-1249;
3. Frier BM. Diabetes Metab Res Rev. 2008;24(2):87-92;
4. Cryer PE. Diabetes. 2008;57(12):3169-3176.

64 year old taxi driver
T2DM x 10 years
No known cardiovascular disease
Weight: 96 KG, Body Mass Index: 30
Heart Rate: 88 BPM
Blood Pressure: 130 / 80mmHG
Fundi normal, Abdo benign
Reduced monofilament sensation both feet
A1C 6.1%;
Creatinine 90 umol/L

Let's come back to Robert

1. Could Robert be having hypoglycemia?
2. What are Robert's risk factors?
3. What would you ask Robert?
4. What will you do about it?
5. Why is hypoglycemia important?

Summary

1. Hypoglycemia remains an underappreciated and important problem for patients with type 2, as well as type 1, diabetes

2. Severe hypoglycemia is associated with a number of potential adverse outcomes including increased cardiovascular risk, dementia, and motor vehicle accidents

3. Even non severe hypoglycemia may be associated with decreased well being, productivity, and treatment adherence as well as increased treatment costs

4. The frequency and impact of hypoglycemia can be minimized with proper patient education and appropriate selection of antihyperglycemic therapies

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